STABLE PHARMACEUTICAL COMPOSITION OF RABEPRAZOLE AND PROCESSES FOR THEIR PREPARATION

Field of the Invention

The technical field of the present invention relates to stable pharmaceutical compositions of rabeprazole, and processes for their preparation.

Background of the Invention

2 - [[[4 - (3-methoxypropoxy) – 3 – methyl - 2-pyridinyl] - methyl] sulfinyl] - 1H - benzimidazole, hereinafter referred to as rabeprazole, belongs to the class of H+ - K+ - ATPase inhibitors. Its intense effect of suppressing gastric acid secretion, and an appropriate duration of action, makes it useful for treatment of various digestive ulcers.

Rabeprazole, however, is prone to rapid decomposition and discoloration in the presence of moisture at neutral to acidic conditions. Conventional stabilizing measures of coating acid sensitive compounds with enteric polymers are unsuitable for rabeprazole because the acidic functional groups of the enteric polymer react with rabeprazole, leading to its decomposition. A subcoating to separate the core and enteric coat is used but decomposition of the rabeprazole nonetheless occurs during the coating stage when the rabeprazole is in contact with coating compositions in commonly used coating equipment, such as fluidized bed coaters. Consequently, other approaches have been attempted to stabilize rabeprazole in pharmaceutical compositions.

For example, U.S. Patent No. 5,035,899 discloses a method of stabilizing a core containing an acid unstable compound. The unstable core is stabilized by layering the core with a subcoat layer, followed by layering with an enteric coat layer. The subcoat layer or the intermediate layer includes a water insoluble film forming material and a suspended, water insoluble fine material.

U.S. Patent Application No. 2002/0039597 discloses a chemically stable pharmaceutical preparation of a benzimidazole type compound in which the preparation is stabilized by incorporating in the core at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, amino alkyl methacrylate copolymer E, arginine aspartate, hydroxypropylcellulose and crospovidone.

Summary of the Invention

In one general aspect there is provided a stable pharmaceutical composition that includes a core. The core includes rabeprazole and at least 10% w/w of low viscosity hydroxypropylcellulose.

Embodiments of the composition may include one or more of the following features. For example, the core may further include an antioxidant. The antioxidant may be one or both of butylated hydroxy toluene and butylated hydroxy anisole. The antioxidant may be from about 0.02% to about 0.2% by weight of the total core weight.

The viscosity of the low viscosity hydroxypropylcellulose may range from about 5 m. Pas to about 300 m. Pas (i.e., 5 cp to about 300 cp). More particularly, the viscosity of the low viscosity hydroxypropylcellulose may range from about 50 m. Pas to about 200 m. Pas.

The core may further include polyvinylpyrrolidone. The average molecular weight of the polyvinylpyrrolidone may range from about 10,000 to about 360,000. More particularly, the average molecular weight of polyvinylpyrrolidone may range from about 40,000 to about 60,000. The polyvinylpyrrolidone may be from about 0.5% to about 5% by weight of the total core weight.

The core may be selected from the group consisting of tablet, granule and capsule and, in particular, may be a tablet. The core may be coated with a subcoat layer and an enteric coat layer. The subcoat layer may be one or more film forming agents. The one or more film forming agents may be one or more of microcrystalline cellulose, carageenan, ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol and xanthan gum and, in particular, may be hydroxypropyl methylcellulose.

The subcoat layer may include an antioxidant. The enteric coat layer may include one or more enteric polymers. The enteric polymer may be one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate; and methacrylic acid copolymers and, in particular, may be hydroxypropyl methylcellulose phthalate.

One or more of the core, the subcoat layer, and the enteric layer may further include one or more pharmaceutically acceptable inert excipients. The one or more pharmaceutically acceptable inert excipients may be selected from the group consisting of binders, disintegrants, lubricants, glidants, diluents, plasticizers, opacifiers, and coloring agents.

In another general aspect there is provided a process for preparing a stable pharmaceutical composition that includes a core. The process includes preparing a core by (i) blending rabeprazole and a low viscosity hydroxypropylcellulose to form a blend, and, one or both of, (ii) granulating the blend and (iii) compressing the blend to form a compact mass core. The low viscosity hydroxypropylcellulose makes up at least 10% w/w of the core.

Embodiments of the process may include one or more of the following features. For example, the viscosity of the low viscosity hydroxypropylcellulose may range from about 5 m. Pas to about 300 m. Pas. The process may further include blending one or more antioxidants with the rabeprazole and low viscosity hydroxypropylcellulose. The antioxidant may be adsorbed over a diluent.

The core may be selected from the group consisting of tablet, granule and pellet and, in particular, may be a tablet. The core may be prepared by one or more of a wet granulation method, a dry granulation method, or a direct compression method and, in particular, the core may be prepared by direct compression method.

The process may further include coating the core with one or both of a subcoat layer and an enteric coat layer. One or both of the subcoat layer and the enteric coat layer may be applied as a solution/suspension. The solution/suspension may be prepared in solvents selected from the group consisting of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof. Alternatively, one or both of the subcoat layer and the enteric coat layer are applied using a hot melt technique.

One or more of the core, the subcoat layer, and the enteric coat layer may contain one or more pharmaceutically acceptable inert excipients.

The one or more pharmaceutically acceptable inert excipients may be selected from the group consisting of binders, disintegrants, lubricants, glidants, diluents, plasticizers, opacifiers, and coloring agents.

In another general aspect there is provided a method of treating digestive ulcers in a mammal by administering to the mammal a stable pharmaceutical composition of rabeprazole. The composition includes a core that includes rabeprazole and at least 10% w/w of low viscosity hydroxypropyl cellulose.

Embodiments of the method may include one or more of the following features and those described above. For example, the viscosity of the low viscosity hydroxypropylcellulose may range from about 5 m. Pas to about 300 m. Pas. The core may further include an antioxidant.

The details of one or more embodiments of the inventions are set forth in the description below. Other features and advantages of the inventions will be apparent from the description and the claims.

Detailed Description of the Invention

We have discovered that a core containing rabeprazole may be stabilized against decomposition by incorporating a stabilizing amount of low viscosity hydroxypropylcellulose (HPC-L) alone or in combination with one or more antioxidants in the core. When used alone, an HPC-L concentration of 10% w/w or more gave improved stability results, as evident below in Table 2.

The use of HPC-L has proved to be useful in preventing the decomposition and discoloration of compositions containing rabeprazole at a concentration of 10% w/w or more of the core. Combining one or more antioxidants with HPC-L helps to improve stability and allows a reduction of HPC-L in the core to an amount of less than 10% w/w. Similarly, incorporating polyvinylpyrrolidone (PVP) in the core has a positive effect on the stability of rabeprazole. Moreover, there is improved stability even with the addition of PVP and a reduction in HPC-L below 10% (w/w). As described in more detail below, these positive effects are evident from the stability data that has been generated over a period of 1 month at 60°C and is contained herein in Tables 1 and 2.

The term "rabeprazole" as used herein includes rabeprazole and its pharmaceutically acceptable salts thereof. The pharmaceutically acceptable salts include salts of rabeprazole with alkali metals such as sodium, potassium, calcium, magnesium and the like. In particular, rabeprazole sodium or rabeprazole potassium may be used.

The term "stable" as used herein refers to chemical stability of rabeprazole in pharmaceutical compositions and indicates a presence of at least 80% w/w of rabeprazole when stored at 60° C for 1 month with respect to the initial amount of rabeprazole as measured, for example, by HPLC.

The term "core" as used herein refers to a compact mass having a definite geometric shape such as tablets, granules, pellets and the like; comprising rabeprazole, HPC-L and, optionally, one or more antioxidants. The core may also contain polyvinylpyrrolidione and other pharmaceutically inert excipients. The core may be prepared by any conventional method known in the art such as wet granulation, dry granulation, direct compression, extrusion-spheronization, moldings and the like.

HPC-L is low viscosity hydroxypropylcellulose which is conventionally used as a binder in low concentrations. It is available in various grades under the trade names Klucel® E, Klucel® G, Klucel® J and Klucel® L., with viscosity varying from about 5 m. Pas to about 300 m. Pas. In particular, Klucel® L (having viscosity of 65 – 150 m Pas.) can be used in the pharmaceutical compositions of stabilized rabeprazole described herein. It is noted that 1 m.Pas. is the same as 1 centipoise (cP).

Examples of antioxidants include lipophilic antioxidants, inorganic antioxidants, and the like. In particular, examples of two suitable antioxidants are butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT). The concentration of the one or more antioxidants may vary from about 0.02% to about 0.2% by weight of the total weight of the core. Although the one or more antioxidants are generally incorporated in the core, optionally, the subcoat may also or instead contain the one or more antioxidant(s) at concentrations of about 0.02% to about 0.5% of the weight of the subcoat.

Polyvinylpyrrolidone (PVP) is a water-soluble polymer that is conventionally used as a binder. The average molecular weight of polyvinylpyrrolidone may vary from about 10,000 to about 360,000. It is commercially available in five viscosity grades identified by their K-value: K-15, K-25, K-30, K-60 and K-90, according to viscosity in ascending order. Polyvinylpyrrolidone K 30 (average molecular weight of 58,000) is particularly useful. The concentration of PVP may vary from about 0.5% to about 5.0% by weight of the total weight of core.

The term "pharmaceutically inert excipients" as used herein includes binders, disintegrants, lubricants, glidants, diluents, plasticizers, opacifiers, coloring agents and the like.

Examples of binders include methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Examples of disintegrants include starch, croscarmellose, crospovidone, sodium starch glycolate and the like.

Examples of lubricants and glidants include colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like.

Examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like.

Examples of plasticizers include acetylated triacetin, triethylcitrate, tributylcitrate, glyceroltributyrate, monoglyceride, poly ethylene glycols, propylene glycol, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethyl phthalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, and the like.

Examples of opacifiers include ferric oxide, titanium dioxide and the like.

Examples of coloring agents include any FDA approved colors for oral use.

The subcoat layer comprises a film-forming agent with or without other pharmaceutically inert excipients. Optionally, the subcoat layer may also contain one or more antioxidants. Examples of film forming agents include microcrystalline cellulose, carageenan, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, polyvinyl alcohol, xanthan gum and the like.

The enteric coat layer includes an enteric polymer with or without other pharmaceutically inert excipients. Examples of enteric polymers include cellulose acetate

phthalate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxy propyl phthalate, hydroxypropyl methylcellulose phthalate (HPMC phthalate), hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L30 D-55, Eudragit® L 100, Eudragit® S 100; and mixtures thereof. A preferred enteric polymer for the purpose of the present invention is HPMC phthalate in a concentration of about 50% to about 90% by weight of the total weight of the enteric coat layer.

As described in greater detail below, in one of the embodiments, there is provided a process for the preparation of a stable tablet of rabeprazole. The process includes preparing a core and coating the core with subcoat and enteric coat layers. Preparing the core includes: (i) blending rabeprazole, HPC-L and, optionally, one or more antioxidants to form a blend, (ii) dry granulating the blend by roller compactor or slugging, (iii) sizing the granules and, optionally, blending with one or more pharmaceutically acceptable inert excipients, and (iv) compressing to form a compact mass. It is this compact mass that is then coated with the subcoat and enteric coat layers.

In another embodiment, there is provided a process for the preparation of a stable tablet of rabeprazole comprising the steps of (a) preparing a core (i) by blending rabeprazole, HPC-L and optionally antioxidant with or without pharmaceutically acceptable inert excipients (ii) forming a wet mass using a granulating fluid or solution/dispersion of pharmaceutically acceptable inert excipient in the granulating fluid (iii) drying and lubricating the granules and (iv) compressing to form a compact mass and (b) coating the core with subcoat and enteric coat layers.

In another embodiment, there is provided a process for the preparation of a stable tablet of rabeprazole comprising the steps of (a) preparing a core by (i) blending rabeprazole, HPC-L and optionally antioxidant with or without pharmaceutically acceptable inert excipients (ii) forming a wet mass using a granulating fluid or solution/dispersion of pharmaceutically acceptable inert excipient in the granulating fluid (iii) passing the wet mass through an extruder equipped with a screen; (iv) spheronizing the extrudate in a spheronizer; (v) drying and sizing the spheroids to form a compact mass and (b) coating the core with sub-coat and enteric coat layers.

In another embodiment, there is provided a process for the preparation of a stable tablet of rabeprazole comprising the steps of (a) preparing a core by (i) blending

rabeprazole, HPC-L and at least one antioxidant adsorbed over a diluent and (ii) compressing to form a compact mass and (b) coating the core with sub-coat and enteric coat layers.

The sub coat layer and enteric coat layer may be applied over the core as solution/suspension of film forming agent or enteric polymer with or without other pharmaceutically inert excipients using any conventional coating technique known in the prior art such as spray coating in a conventional coating pan or fluidized bed processor; or dip coating.

Alternatively, coating can also be performed using hot melt technique whenever possible.

The solvents used for coating processes or for granulation may be selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention any way.

EXAMPLE 1-8

The core tablet compositions for Examples 1-8 are listed in Table 1. The results of the stability evaluation of core compositions for Examples 1-8 over a period of 1 month at 60^0C are listed in Table 2.

The preparation of the core tablets of Examples 1-3 involved the following steps:

1. Rabeprazole sodium, mannitol, low substituted-HPC, HPC-L and magnesium oxide were mixed together to form a uniform blend.
2. The blend of step 1 was lubricated by mixing with magnesium stearate.
3. The final lubricated blend of step 2 was directly compressed into core tablets using suitable size punches.

The preparation of the core tablets of Examples 4-8 which incorporates an antioxidant, involved the following steps:

1. BHA and/or BHT was dissolved in isopropyl alcohol, adsorbed over mannitol, and dried in a fluidized bed dryer at room temperature.

2. Rabeprazole sodium, BHA and/or BHT coated mannitol, low substituted-HPC, L-HPC and magnesium oxide were mixed together to form a uniform blend.
3. The blend of step 2 was lubricated by mixing with magnesium stearate.
4. The final lubricated blend of step 3 was directly compressed into core tablets using suitable size punches.

Table 1. Compositions of the core tablets (Examples 1-8).

Example No.	1	2	3	4	5	6	7	8
Rabeprazole Sodium	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Mannitol	118.25	113.75	106.25	113.6	113.6	113.45	107.45	105.95
Magnesium oxide	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
L-HPC	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
HPC-L	3mg	7.5mg	15mg	7.5mg	7.5mg	7.5mg	7.5mg	15mg
BHA	-	-	-	0.15mg	-	0.15mg	0.15mg	0.15mg
BHT	-	-	-	-	0.15mg	0.15mg	0.15mg	0.15mg
Isopropyl alcohol	-	-	-	q.s	q.s	q.s	q.s	q.s
Polyvinylpyrolidone	-	-	-	-	-	-	6mg	-
Magnesium stearate	0.75mg	0.75mg	0.75mg	0.75mg	0.75mg	0.75mg	0.75mg	0.75mg
Core Tablet weight	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg

Table 2. Results of stability evaluation of core tablets (Examples 1-8) as percentage (w/w) rabeprazole content, over a period of 1 month at 60^0C.

Example No.	1	2	3	4	5	6	7	8
Initial	99.56	99.34	99.35	99.46	99.87	99.26	99.27	99.67
After 1 month at 60^0C	70.68	79.97	90.77	82.98	83.79	84.92	87.28	92.09

The above core tablets of Examples 1-8 were coated with the sub coat layer and enteric coat layer using the following coating compositions:

(i) Sub coat layer

Hydroxypropylmethyl cellulose	26.06 mg
Polyvinyl pyrrolidone	0.53 mg
Titanium dioxide	0.46 mg
Ferric oxide yellow	0.07 mg
Propylene Glycol	3.91 mg
Water.	q.s.

(ii) Enteric coat layer

HPMC Phthalate 55	13.04 mg
Triacetin	1.46 mg
Talc	4.09 mg
Ferric oxide yellow	0.02 mg
Titanium dioxide	0.72 mg
Acetone	q.s.

Procedure:

A. The coating of the core tablets of Examples 1 – 8 with the sub coat layer involved the following steps-

1. Color and titanium dioxide were added in propylene glycol and thoroughly mixed to obtain a homogenous dispersion.
2. Hydroxypropyl methylcellulose and polyvinylpyrrolidone were added in water and mixed thoroughly to obtain a uniform dispersion.
3. The dispersion of step 1 was added to the dispersion of step 2 with stirring to obtain the final sub coat dispersion.
4. Core tablets obtained above were loaded in Freund Hi-Coater and coated with the final dispersion of step 3 until the desired weight build up was achieved, followed by drying if required.

B. The enteric coating of the subcoated tablet involved the following steps-

1. Triacetin was dispersed in part of the acetone followed by the addition of HPMC Phthalate and continuous stirring until a clear solution was obtained.
2. Color, titanium dioxide and talc were added to the remaining part of the acetone and thoroughly mixed to obtain a uniform dispersion.

3. The dispersion of step 2 was added to the solution of step 1 with continuous stirring to obtain the final coating dispersion.
4. Sub coated tablets were loaded in a Freund Hi-Coater and coated with the final dispersion of step 3 until the desired weight buildup was achieved, followed by drying wherever required.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.